REMARKS

Claims 1-2, 5, 7-15 and 49 were examined in the pending Office Action, the remaining claims having been cancelled or withdrawn subsequent to a Restriction Requirement.

Claim 1 has been amended herein to remove the word "having" when referring to an addition variant of SEQ ID NO:7 wherein 1-4 amino acids are added to either terminus. Part (b) of the claim was visually subdivided into (i) SEQ ID NO:7 and (ii) the addition variant of SEQ ID NO:7 for greater clarity. Finally,, the biological activity of the pentapeptide or addition variant of (b) is defined in terms of the biological activity (transition metal ion binding; plasminogen binding) of human or rabbit HPRG or, newly added, of a polypeptide the sequence of which is SEQ ID NO:5 or 6.

Claims 1-2, 5, 7-15 and 49 remain active in this case. Claims 3, 4, 16-48 and 50—55 remain withdrawn. Cancellation of the withdrawn claims will await the indication by the Office that the pending claims are patentable and that no rejoinder of any withdrawn claims will be considered.

It is submitted that no new matter has been introduced by the present amendments and entry of the same is respectfully requested. The Office Action and cited references have been considered. Favorable reconsideration is respectfully requested. Applicants respectfully submit that, in view of the present amendments and remarks, their application is now in condition for allowance.

I. Withdrawal of Objections and Rejections

Applicants note and thank the Examiner for withdrawal of the previous objections and rejections as set forth in paragraphs 6-11 of the Action. In particular, these withdrawn rejections include:

(1) several rejections under 35 U.S.C. 112, second paragraph;

(2) the rejection of claims 1-2, 5, 7-15 and 49 under 35 U.S.C. 112, first paragraph (written description);

(3) the rejection of claims 1, 5-15 and 49 under 35 U.S.C. 102(e) over Olsson *et al.* (as evidenced by Koide *et al.* and Borza *et al.*);

(4) the rejection of claims 1-2, 11, 13 and 49 under 35 U.S.C. 102(b) as being anticipated by "Borza-1" (see below) as evidenced by Donate *et al.* (*Canc Res 64*:5812-17, 2004); and

(5) the rejection of claims 1-2, 5, 7-15 and 49 under 35 U.S.C. 103(a) as being obvious over Borza-1, in view of "Azizkhan" and "Simantov" (see below).

II. FORMAL OBJECTIONS AND APPLICANTS RESPONSE

A. Presence of Embedded Hyperlinks

Both potential nyperlinks in the specification have been modified by amendment as required by the Office Action.

B. Notation of Benefit Claim to Priority Application

The first line of the specification has been amended to claim priority to a U.S. provisional application as required by the Office.

C. Extraneous (Inadvertent) Phrase

Applicants thank the Examiner for catching a phrase that was inadvertently included in th8es specification at page 28, lines 4-5. This phrase was accidentally and inadvertently left in the specification and was not intended to be included. This phrase is being deleted.

D. The Use of the Trademarks

Applicants note the Office's comments on trademarks in the specification. Since these are not part of, or their meaning (as tradename vs a generic term) is not directly relevant to the present claims, Applicants believe they may be left as is.

E. Defective Oath/Declaration

The oath or declaration was considered defective. because it allegedly did not identify the citizenship of inventor Fernando Donãte. Applicants will file a Substitute Declaration under separate cover in the name of the indicated inventor showing his citizenship.

III. NEW REJECTION UNDER § 102 AND APPLICANTS' RESPONSE

Claims 1-2, 11, 13 and 49 were rejected under 35 U.S.C. 102(b) as being anticipated by Borza *et al., Biochemistry 35*:1925-34, 1996 ("Borza-1"). Applicants note that claims 5, 7-10, 12 and 14 (all claims that involve a labeled peptide are free of this rejection

First Basis for § 102 Rejection over Borza-1

According to the Action, these claims were interpreted as being drawn to an anti-angiogenic polypeptide or peptide consisting of the sequence (His/Pro)-(His/Pro)-Pro-His-Gly (SEQ ID NO:7) or an addition variant thereof **having** an additional 1 to 4 amino acids selected from His, Pro or Gly at the N- or C-terminus of the pentapeptide.

The Office interpreted the term ***"having"*** is being interpreted as equivalent to ***"comprising"*** (open-ended). Borza-1 was said to teach the H/P domain from human and rabbit (referred to below as "hum/rabb") HPRG, which the Office thus interpreted as:

> an addition variant polypeptide or peptide of SEQ ID NO:7 consisting of SEQ ID NO:7 and ***having*** an additional 1 to 4 amino acids (His, Pro or Gly) at the N- or C-terminus of SEQ ID NO:7,

This claim is therefore viewed as reading on the "complete" hum/rabb H/P domain (with the Action pointing to the entire Borza-1 document, but particularly Figs 2-4, Table 1 and page 1927, right column). The Action went on to comment that

> ...products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present...

citing *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) and MPEP 2112.01.

The Action concluded that the H/P domain of hum/rabb HPRG as taught by Borza-1, and interpreted to "consist of SEQ ID NO:7" and "'**having**' an additional 1 to 4 amino acids selected from His, Pro or Gly at the N- or C-terminus of SEQ ID NO:7" necessarily possesses the claimed properties and anticipated claim 1 (and various of its dependent claims).

Applicants' Response

Claim 1 has been amended to remove the "open ended" language of having, which was inadvertent and did not indicate applicants' intended claim scope. The amended claim states that the isolated anti-angiogenic polypeptide or peptide is "a pentapeptide consensus subsequence from SEQ ID NO:5 or 6 ***consisting of***

(i) the sequence (His,Pro)-(His,Pro)-Pro-His-Gly (SEQ ID NO:7), or

(ii) an addition variant of SEQ ID NO:7 to which are added at the N- or C-terminus, 1 to 4 amino acids selected from His, Pro and Gly"

This claim language can no longer be interpreted in the same way as the prior language, and does not read on the "complete" hum/rabb H/P domain disclosed in Borza-1. In view of this amendment, it would be proper to withdraw this ground for rejection.

Second Basis for § 102 Rejection over Borza-1

The Borza-1 reference was also said to anticipate the above anti-angiogenic polypeptide or peptide together with a pharmaceutically acceptable carrier in a pharmaceutical composition suitable for injection. This was based on the Office's interpretation of the disclosure in this reference of the H/P domain of rabbit HPRG in *5 mM phosphate buffer, pH 7.2.* The Office alleged that this buffer is "reasonably interpreted to be a pharmaceutically acceptable carrier and in suitable form for injection" (citing see page 1926, right col).

Applicants' Response

First, because of the amendment of claim 1 as discussed above, the pharmaceutical composition claims no longer can be viewed as reading on the H/P domain of rabbit HPRG. Second, Applicants disagree with the interpretation that 5 mM phosphate buffer is a pharmaceutically acceptable carrier. This buffer is not pharmaceutically acceptable because it is not isotonic. Direct injection of such a solution would induce an injection site reaction and possible local vasospasm. Also, the claimed peptide would have to be stable in a pharmaceutically acceptable carrier, and this references does not teach that the peptide would be stable in this buffer.

For the foregoing reasons, this basis for rejecting the claims may properly be withdrawn.

Third Basis for § 102 Rejection over Borza-1

The Action turns to claim 49, directed to an affinity ligand that comprises the polypeptide or peptide of claim 1 or 2 immobilized to a solid support or carrier. The Action refers to a disclosure in Borza-1 of the H/P domain of rabbit HPRG "bound" to a DEAE-cellulose column (interpreted as a "solid support") and interprets this as an affinity ligand useful for binding to or isolating an HPRG-binding molecule (citing paragraph bridging pgs 1928-29).

Applicants' Response

Again, because of the amendment of claim 1 as discussed above, the pharmaceutical composition claims no longer can be viewed as reading on the H/P domain of rabbit HPRG. Second, Applicants strongly disagree with the interpretation that DEAE is an affinity ligand. Indeed, this disclosure describes how the protein was purified using a standard ion-exchange chromatographic material. Those of skill in the art know well that a protein is not immobilized to DEAE. This is simply an over-interpretation or misinterpretation of the technology. Therefore, this ground for rejection should be withdrawn.

In conclusion, , it should be apparent that Borza-1 does not anticipates the indicated claims as amended and all grounds for rejection over this reference may properly be withdrawn..

IV. NEW REJECTIONS UNDER 35 U.S.C. § 103(A)

A. First New Rejection for Obviousness

All pending claims (1-2, 5, 7-15 and 49) were rejected as being obvious in view of Borza-1 (as characterized above) in combination with

(1) Azizkhan *et al., J Exp Med 152*:931-44, 1980 (**"Azizkhan"**) , and

(2) Borza *et al., J Biol Chem 273*:5493-99, 1998 **("Borza-2")** and

(3) Simantov *et al.* (US 2001/0041670 A1, 12/6/1999, (**"Simantov"**)

These references had been cited in earlier Actions or in Applicants' IDS

The interpretation of claims 1-2, 11, 13 and 49 were discussed above in connection with the §102 rejection. Accordingly, that interpretation no longer applies to these claims in view of the amendment.

Claims 5, 7-10, 12, 14 and 15 are drawn to the claimed polypeptides/peptides that are labeled (diagnostically or therapeutically) and to a therapeutic anti-angiogenic pharmaceutical composition comprising the claimed peptides (in which the peptide is bound to a therapeutically active moiety and combined with a pharmaceutically acceptable carrier.

The Action admits that Borza-1 admittedly does not teach any of the labeled polypeptides of these claims (noting that Borza is directed to the broader H/P domain of hum/rabbit HPRG). The Action asserts that these deficiencies are "made up for" in the teachings of Azizkhan and Simantov.

Azizkhan allegedly teaches (the entire document, particularly the abstract) that:

(1) heparin secreted by mast cells stimulates capillary EC migration, which is an important component of angiogenesis *in vivo* and

(2) the migratory activity of heparin was blocked by heparin specific antagonists (citing to the entire document, particularly the abstract).

Borza-2 allegedly teaches (the entire document, particularly page 5493, 2nd col.) that:

(1) the His residues in the H/P domain of HPRG mediate interactions with heparin, transition metals and heme, and

(2) interaction with heparin-binding proteins is largely electrostatic but requires Lys or Arg side chains in other known cases, and

(3) heparin's anticoagulant effect is of obvious pharmacological interest (citing to the entire document, particularly page 5493, 2nd col.).

Simantov allegedly teaches

(1) pharmaceutical compositions comprising an HPRG polypeptide and a pharmaceutically acceptable carrier (citing to page 3, para's [0039-0040] and page 6 para [0084]), and

(2) various diagnostic and therapeutic labels including radionuclides, fluorescein, rhodamine, Texas red and phycoerythrin as well as others (citing to pages 10 and 13, para [0174]).

The Office concluded that it would have been *prima facie* obvious to have produced compositions comprising diagnostically or therapeutically labeled human or rabbit H/P domain (*i.e.*, SEQ ID NO:7 addition variant – ***again based on the previous scope of claim 1***) of HPRG as taught by Borza-1 to detect secreted heparin as an angiogenesis marker or inhibit angiogenesis or migration of capillary ECs to block heparin stimulated capillary EC migration. The Office found the requisite motivation and reasonable expectation of success in the teachings of Borza-1 and Azizkhan and Borza-2 and Simantov based in part on the interpretation of Borza-1 regarding the H/P domain of hum/rabb HPRG, which binds heparin, along with the above-noted disclosure in Azizkhan, Borza-2 and Simantov.

The Action states further that it would have been *prima facie* obvious to label the H/P domains (per Borza-1) (interpreting claim 1 broadly prior to the present amendment) diagnostically or therapeutically with the diagnostic and therapeutic labels taught by Simantov to

detect secreted heparin as an angiogenesis marker or to block the migratory activity of heparin and hence, angiogenesis or migration of capillary ECs.

Finally, according to the Office, one of ordinary skill in the art would have been motivated to combine the diagnostically/therapeutically labeled H/P domain (interpreting claim 1 broadly prior to the present amendment) with a pharmaceutically acceptable carrier to facilitate therapeutic administration of the labeled polypeptides. Thus, it would have been *prima facie* obvious to have produced compositions comprising diagnostically or therapeutically labeled hum/rabb H/P domains of HPRG (interpreting claim 1 broadly prior to the present amendment) to detect secreted heparin as an angiogenesis marker and inhibit angiogenesis or migration of capillary ECs to block heparin stimulated capillary EC cell migration in view of the teachings of Borza-1 and Azizkhan and Borza-2 and Simantov

Applicants' Response

Applicants believe that in view of the amendments, the primary reference Borza-1 is no longer applicable to claims of the present scope, so that the entire ground for rejection over the combination of that primary reference with three secondary references is also not applicable to the amended claims.

In addition, Applicants believer there is a fundamental misunderstanding in the Office's position because HPRG does not mediate its antiangiogenic effects through the binding to heparin or through the modulation of endothelial cell migration. The inventors and their collaborators showed that HPRG actually induced apoptosis in endothelial cells (Juarez et al. (2002) *Cancer Res. 62(18)*:5344-50). The antiangiogenic activity of HPRG is mediated by binding to cell surface tropomyosin – not to heparin. The present claims are not based on a biological activity of heparin-stimulated migration. HPRG has pleiotropic activities and does many things, but the claimed peptides and their activity would not have been obvious to one skilled in the art at the time the present invention was made.

In view of the foregoing remarks, it would be proper to withdraw all the above-noted grounds for rejection based on § 103(a).

B. Second New Rejection for Obviousness

Claims 1, 5, 7-15 and 49 (*i.e.*, all pending claims but claim 2) were further rejected as being obvious over Borza-1 in view of the same three secondary references.

This rejection is based on the interpretation of claim 1 as discussed in the section concerning the § 102 rejection over Borza-1 and relates to (i) the anti-angiogenic polypeptide or peptide (interpreted broadly prior to the present amendments) , the labeled (diagnostically or therapeutically) hum/rabb H/P domain variants (having the same broad interpretation), (iii) pharmaceutical composition comprising the anti-angiogenic polypeptide/peptide (interpreted broadly) in combination with a pharmaceutically acceptable carrier, and (iv) the anti-angiogenic polypeptide/peptide (interpreted broadly) immobilized to a solid support or carrier.

The interpretation of claim 1 in view of Borza-1 is discussed above. The deficiencies of this reference as to diagnostically or therapeutically labeled polypeptides (interpreted as the H/P domain of human or rabbit HPRG) an acceptable carrier in suitable form for injection are allegedly supplied by Azizkhan and Borza-2 and Simantov. Azizkhan and Borza-2 are cited for reasons discussed above.

Simantov allegedly teaches (1) HPRG and functional variants comprising conservative amino acid substitutions, (2) pharmaceutical compositions comprising the HPRG polypeptides and a pharmaceutically acceptable carrier and (3) various diagnostic and therapeutic labels including radionuclides, fluorescein, rhodamine, Texas red and phycoerythrin as well as others.

According to the Action, it would have been *prima facie* obvious to have produced compositions comprising diagnostically or therapeutically labeled conservative amino acid variant H/P domains of human or rabbit HPRG for detection of secreted heparin as an angiogenesis marker or inhibit angiogenesis or migration of capillary endothelial cells to block heparin stimulated capillary endothelial cell migration. The motivation and expectation of success for producing the claimed diagnostically or therapeutically labeled compositions of a conservative amino acid variant H/P domains for detection of secreted heparin as an angiogenesis marker or to inhibit angiogenesis or migration of capillary ECs or to block heparin-stimulated capillary EC migration presumably come from the teachings of Borza-1, Azizkhan and Borza-2 and Simantov. This too was discussed above. According to the Office one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to produce conservative amino acid hum/rabb H/P domain variants, which were known to mediate heparin interaction (*i.e.*, His, Lys or Arg substitutions). There would have been an advantage to label the H/P domain conservative amino acid substitution variants with the diagnostic and therapeutic labels disclosed

in Simantov for detection of secreted heparin as an angiogenesis marker or for inhibition of angiogenesis or migration of capillary ECs. Further, one would have been motivated to combine the therapeutically labeled H/P domain conservative substitution variants with a pharmaceutically acceptable carrier to facilitate therapeutic administration of the labeled polypeptides. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicants' Response

For the sake of brevity, Applicants reiterate their earlier remarks concerning the first obviousness rejection. In view of the amendment of claim 1, the claims are free of the Borza-1 primary reference, and thereby, are also free of the combination of the additional references. Applicants reiterate their points about the inapplicability of the relevance of the detection of secreted heparin as a marker, as discussed by Simantov, and adopted by the Office, to the present claims.

In view of the foregoing remarks, it would be proper to withdraw all the above-noted grounds for rejection based on § 103(a).

V. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that all the present claims are free of the cited prior art and therefore in condition for allowance, and respectfully requests early notice of such favorable action.

If in the Office's view, the claims are not free of the cited art, Examiner Blanchard is respectfully requested to contact the undersigned at (202) 628-5197 to see if this can be remedied rapidly, for example by either Applicants' or Examiner's Amendment.

Respectfully submitted,

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